IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	Hans BIGALKE and Jürgen FREVERT
Serial No.:	10/018,373
Filed:	December 6, 2001
For:	Therapeutic Composition Comprising a Botulinum Neurotoxin
Art Unit:	1645
Examiner:	Vanessa L. FORD

REPLY BRIEF ON BEHALF OF APPELLANT UNDER 37 CFR §§ 41.50(b) AND 41.50(b)(1)

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INTRODUCTORY COMMENTS

Further to the DECISION ON APPEAL, dated May 21, 2010, Appellant hereby amends independent Claim 16 and requests reconsideration and withdrawal of the rejection of Claims 16-18, which claims are newly rejected pursuant to 37 CFR § 41.50(b).

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STATUS OF CLAIMS

Claims 11-18 are pending in the application. In accordance with 37 CFR § 41.50(b)(1), independent Claim 16 is presently amended. The status of the claims is as displayed in the claims appendix attached hereto.

GROUNDS OF REJECTION

Under 37 CFR § 41.50(b), the Board in its Decision on Appeal dated May 21, 2010 articulated a new ground of rejection under 35 U.S.C. § 103(a). Thus, there is one remaining ground of rejection in this application. The rejection is as follows:

(A) whether Claims 16-18 are unpatentable under 35 U.S.C. § 103(a) over *Göschel, et al.*, (Experimental Neurology 1997, 147:96-102) in view of *Johnson, et al.* (U.S. Patent No. 5,512,547, published April 30, 1996).

The rejection by the Board is based on the *Göschel, et al.* teaching of administering botulinum toxin in a method of treating a dystonia, or a nervous system disorder treatable with botulinum toxin to subjects who may have low levels of neutralizing antibodies present but still respond to treatment. *Johnson, et al.* is cited for teaching compositions of pure botulinum toxin that are free from non-complexing proteins. The Board concludes that based on the *Göschel, et al.* disclosure of patients who exhibit low levels of neutralizing antibodies and still respond to treatment, it would have been obvious to use the purified toxin of *Johnson, et al.* for further treatment in such patients.

APPELLANT'S AMENDMENT UNDER 37 CFR § 41.50(b)(1)

(A) Rejection of Claims 16-18 under 35 U.S.C. § 103(a) over *Göschel, et al. (Experimental Neurology 1997, 147:96-102) in view of Johnson, et al. (U.S. Patent No. 5,512,547, published April 30, 1996).*

In accordance with 37 CFR § 41.50(b)(1), Appellant hereby submits an appropriate amendment of the claims so rejected.

Claim 16 is amended to define the human or animals already exhibiting neutralizing antibodies against botulinum neurotoxin complexes to be "secondary non-responders". Please see the Listing of Claims which incorporates the instant amendment in the CLAIMS APPENDIX attached hereto.

Secondary non-responders are defined in the instant Specification at page 5. The inventors explain that patients who have developed an antibody titer against botulinum toxin complexes are no longer amenable to further treatment because administration of the toxin complexes no longer alleviates the symptoms. Such affected patients are identified as "so-called secondary non-responders". Literal support for the amendment, drawn to the treatment of secondary non-responders, may also be found in the instant Specification at page 8, last paragraph. Further support for the instant amendment may be found in Example 7, at page 15, and Example 8, at page 16. No new matter is introduced with the instant amendment.

Generic Claim 16 is presently amended to be drawn to a method of treating a human or animal with dystonia or a nervous system disorder treatable with a botulinum neurotoxin, comprising administration, to the human or animal, a treatment effective amount of a botulinum neurotoxin from *Clostridium botulinum* of type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins,

wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins, and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes and is a secondary non-responder.

Appellant submits that the cited art, *Göschel, et al.* and *Johnson, et al.*, do not teach or suggest the instant claim limitation to administering a botulinum neurotoxin to a human or animal "wherein the human or animal already exhibits neutralizing antibodies against neurotoxin complexes and is a secondary non-responder".

Göschel, et al. teach that neutralizing antibodies were present in all nonresponders, and that all patients from various clinics who had been treated unsuccessfully with the toxin had neutralizing antibodies. (See *Göschel, et al.*, abstract). *Göschel, et al.* teach that neutralizing antibodies are the cause of therapeutic failure. (See *Göschel, et al.* at page 101, left column). Thus, *Göschel, et al.* teach that botulinum toxin treatment in subjects who already exhibit neutralizing antibodies and who are secondary non-responders, i.e. patients who had been treated unsuccessfully, is not effective.

Furthermore, *Göschel, et al.* teach that, "Therefore, a patient who develops immunity would possibly be denied treatment for the rest of his life." (See *Göschel, et al.* at page 102, first paragraph). Moreover, with regard to the presence of botulinum toxin specific antibodies in patients, *Göschel, et al.* teach that, "As a rule, this necessitates the termination of treatment." (See *Göschel, et al.*, abstract). Thus, *Göschel, et al.* teach discontinuing botulinum neurotoxin therapy in patients who develop immunity and who are secondary non-responders, and thus, teach away from administering botulinum neurotoxin to secondary non-responders.

Moreover, Appellant submits that with regard to immunity by patients, *Johnson, et al.* teaches that, "This renders treatment of the various muscle disorders with botulinum toxin ineffective". (See *Johnson, et al.* at Column 1, lines 49-55).

Appellant submits that the cited art is completely silent with respect to teaching or suggesting administering a botulinum neurotoxin free of complexing proteins to a human or animal "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes and is a secondary non-responder" as instantly claimed.

Appellant further submits that the cited art teach that the presence of botulinum toxin specific antibodies in a patient necessitates the termination of treatment, and therefore, teaches away from administering botulinum neurotoxin in patients who exhibit botulinum specific antibodies.

Therefore, the rejection should be withdrawn for failing to demonstrate all claim limitations to be taught or suggested by the art.

Moreover, Appellant submits that the cited art do not provide an expectation of success for practicing the claimed methods.

Significantly and critically, the art of record in the instant application teaches that the treatment of subjects already exhibiting neutralizing antibodies against botulinum neurotoxin complexes and who are secondary non-responders, would <u>not</u> be successful.

Johnson, et al. teach that, "A major drawback to the use of botulinum toxin in treatment of hyperactive muscle disorders is development of antibodies or other types of immunity by patients. The toxin is recognized by patient's immune

systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." (See Column 1, lines 49-55, emphasis added.)

Moreover, this teaching in *Johnson, et al.* is acknowledged by the Board to evidence that a person of skill in the art would not have reasonably expected success in treating a patient already exhibiting neutralizing antibodies against botulinum neurotoxin complexes. (See the Decision on Appeal at page 7).

Göschel, et al. teach that neutralizing antibodies were present in all nonresponders and that all patients from various clinics who had been treated unsuccessfully with the toxin had neutralizing antibodies. (See *Göschel, et al.*, abstract). *Göschel, et al.* teach that neutralizing antibodies are the cause of therapeutic failure. (See *Göschel, et al.* at page 101, left column). With regard to the presence of botulinum toxin specific antibodies in patients, *Göschel, et al.* teach that, "As a rule, this necessitates the termination of treatment." (See *Göschel, et al.*, abstract). Furthermore, *Göschel, et al.* teach that, "Therefore, a patient who develops immunity would possibly be denied treatment for the rest of his life." (See *Göschel, et al.* at page 102, first paragraph).

Moreover, the Office acknowledges that the art of record in the instant application, in particular, *Kessler, et al.* (J. Neurol. 246:265-274, 1999), teach that "secondary nonresponse is one of the major problems in long-term treatment of CD with botulinum toxin A because it entails discontinuing, depriving the patient of the most successful therapy available (page 272)." (See Examiner's Answer at page 37 and the Decision on Appeal at page 7).

Thus, the art of record in the instant application teaches that the presence of neutralizing antibodies against botulinum neurotoxin in a subject renders botulinum toxin treatment ineffective, and that subjects who already exhibit

neutralizing antibodies against botulinum neurotoxin complexes and who are secondary non-responders no longer derive a therapeutic effect from *Clostridium botulinum* toxin therapy, and therefore, botulinum toxin therapy should be discontinued.

The cited art, *Göschel, et al.* and *Johnson, et al.*, do not provide any evidence that a person of ordinary skill in the art would have reasonably expected a subject who already exhibits neutralizing antibodies against botulinum neurotoxin complexes and who is a secondary non-responder, to respond to a purified toxin as taught in *Johnson, et al.*

In view of the foregoing, Appellant submits that the cited *Göschel, et al.* and *Johnson, et al.* do not provide a reasonable expectation of successfully treating a human or animal by administering a *Clostridium botulinum* neurotoxin which is free from complexing proteins to a human or animal who already exhibits neutralizing antibodies to botulinum neurotoxin complexes and is a secondary non-responder as instantly claimed.

CONCLUSION

In summary, Appellant respectfully requests consideration of Appellant's amendment and rebuttal arguments and evidence which, when properly considered as required by the case law, rebut any *prima facie* rejection for obviousness.

Therefore, Appellant submits that the obviousness rejection should be withdrawn. Allowance is solicited.

If necessary, the Commissioner is hereby authorized to charge any further or additional fees which may be required (due to omission, deficiency, or otherwise), or to credit any overpayment, to Deposit Account No. 08,3220.

Respectfully submitted:

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By: _____

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CLAIMS APPENDIX

Listing of Claims Involved in the Appeal.

Claims 1-10: (canceled)

Claim 11. (previously presented) A method of treating a human or animal with a cosmetic condition treatable with a botulinum neurotoxin, comprising administration, to the human or animal, a treatment effective amount of a botulinum neurotoxin from *Clostridium botulinum* of type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins, and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Claim 12. (previously presented) The method of claim 11 wherein the subject exhibits neutralizing antibodies against a complex of *Clostridium botulinum* type A or B or a complex of *Clostridium botulinum* type A and type B.

Claim 13. (previously presented) The method of claim 11 wherein the cosmetic treatment is for hyperhidrosis.

Claim 14. (previously presented) The method of claim 11 wherein the cosmetic treatment is for wrinkling.

Claim 15. (previously presented) The method of claim 14 wherein the cosmetic treatment is for facial wrinkling.

Claim 16. (currently amended) A method of treating a human or animal with dystonia or a nervous system disorder treatable with a botulinum neurotoxin, comprising administration, to the human or animal, a treatment effective amount of a botulinum neurotoxin from *Clostridium botulinum* of type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins, and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes and is a secondary non-responder.

Claim 17. (previously presented) The method of claim 16 wherein the subject exhibits neutralizing antibodies against a complex of *Clostridium botulinum* type A or B or a complex of *Clostridium botulinum* type A and type B.

Claim 18. (previously presented) The method of claim 16 wherein the dystonia or disorder of the nervous system is selected from spasmodic torticollis, blepharospasm, spasticities such as footdrop, hemifacial spasms, migraine, low back pain, cervical spine disorders and hypersalivation.